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| TO: | Examiner Nancy Vogel<br>ART UNIT 1661 | FROM: | SHELLY GUEST CERMAK |
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| App. No.: | **10/673,860** | DATE: | November 30, 2005 |

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1) This Facsimile Cover Sheet (1 pg)
2) Appeal Brief Transmittal Cover Sheet (1 pg)
3) Brief for Appellant, with Appendices A-C (13 pp)
4) PTO-2038 (1 pg)

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November 30, 2005

Atty. Docket No. US-111

In re application of: Kikuchi et al.
Application. No.: 10/673,860
Filing Date: September 30, 2003
Title: Methods for Secretory Production of Proteins

**Mail Stop Appeal Brief - Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA. 22313-1450

Sir:
Transmitted herewith is an Appeal Brief in the above-identified application.

☒ The fee under 37 CFR 1.17(c) for filing a brief in support of an appeal is enclosed.
☐ The fee under 37 CFR 1.17(d) to request for oral hearing is enclosed.
☐ An extension of time petition and the request fee of for months is enclosed.

The above fees are submitted via the following payment method:

☐ Please charge Deposit Account No. _____ in the amount of $ .
☐ A check in the amount is enclosed, including to cover any extension of time fee.
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  ☐ Any filing fees under 37 C.F.R. § 1.16 for the presentation of extra claims.
  ☐ Any patent application processing fees under 37 C.F.R. § 1.17.
  ☐ Any Extension of Time fee.

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Respectfully submitted,

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Date: November 30, 2005

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re application of: | |
| Kikuchi et al. | Art Unit: 1661 |
| Application No.: **10/673,860** | Examiner: Nancy Vogel |
| Filing Date: 30 September 2003 | Attorney Ref. No.: US-111 |
| For: METHODS FOR SECRETORY PRODUCTION OF PROTEINS | |

**BRIEF FOR APPELLANT**

**Mail Stop Appeal Brief - Patents**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

COMES NOW the Appellant to present this Brief in support of the appeal of the final rejection of Claims 1, 3, 4, 7, 8, 10, and 11 contained in the Office Action dated June 3, 2005 ("Final Rejection") in the above-captioned patent application. A petition for an extension of time is not necessary, as the Notice of Appeal was timely filed on September 30, 2005 with a petition for a one-month extension of time, and this appeal is filed with 2 months of the filing of the Notice of Appeal.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. If, however, additional extensions of time are necessary to prevent abandonment of this application or dismissal of this appeal, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is hereby authorized to charge fees necessitated by this paper, and to credit all refunds and overpayments, to the credit card authorized on the attached PTO-2038.

For the following reasons, Appellant respectfully submits that the final rejection of each of Claims 1, 3, 4, 7, 8, 10, and 11 in this application is in error, and therefore respectfully requests reversal of the rejections.

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## TABLE OF CONTENTS

## I. Real Party in Interest

The real party in interest is Ajinomoto Co., Inc, a corporation of Japan.

## II. Related Appeals and Interferences

There are no related appeals or interferences.

## III. Status of Claims

Claims 1 and 3-12 are pending. Claims 5, 6, 9, and 12 are withdrawn from consideration. No claims have been identified in the Final Rejection as being in condition for allowance. Claims 1, 3, 4, 7, 8, 10, and 11 stand finally rejected in the Final Rejection dated 03 June 2005, and are on appeal.

## IV. Status of Amendments

All amendments to the claims have been entered.

## V. Summary of Invention

The present invention relates to a method for producing a heterologous protein comprising culturing a *Corynebacterium glutamicum* AJ12036 (FERM BP-734) bacterium or mutant thereof having a genetic expression construct comprising a nucleic acid sequence encoding a signal peptide region from a coryneform bacterium which is downstream of a promoter sequence which functions in a coryneform bacterium, and a nucleic acid sequence encoding a heterologous protein which is downstream of said nucleic acid sequence encoding said signal peptide region, and recovering said heterologous protein, wherein said bacterium or mutant thereof is able to secrete the heterologous protein at least 2-fold higher than *Corynebacterium glutamicum* ATCC13869 having said genetic expression construct (see original claim 2 and paragraph [0027], for example).

The present invention also relates to the above-described bacterium or mutant thereof, wherein said mutant does not produce a cell surface protein (see paragraph [0027], for example).

The present invention also relates to the above-described bacterium or mutant thereof, wherein said signal peptide region comprises a signal peptide of a cell surface protein from a coryneform bacterium (see paragraph [0032], for example).

The present invention also relates to the above-described bacterium or mutant thereof, wherein said signal peptide region comprises a signal peptide of a cell surface protein from *Corynebacterium ammoniagenes* (see paragraph [0032], for example).

The present invention also relates to the above-described bacterium or mutant thereof, wherein said signal peptide comprises the amino acid sequence of SEQ ID NO: 3 (see paragraph [0032], for example).

The present invention also relates to the above-described bacterium or mutant thereof, wherein said culturing of said bacterium or said mutant thereof is conducted in a medium containing at least 0.25 g/l (2.25mM) of calcium ion (see paragraph [0151] and table 7, for example).

The present invention also relates to the above-described bacterium or mutant thereof, wherein said culturing of said bacterium or said mutant thereof is conducted by controlling the dissolved oxygen concentration at 3% or less (see paragraph [0152] and table 8, for example).

## VI. Issues

A. Whether Claims 1, 3, 4, 7, 8, 10, and 11 are unpatentable under 35 U.S.C. § 112, 1st paragraph, for a lack of an adequate written description.

## VII. Grouping of Claims

A. For the rejections of Claims 1, 3, 4, 7, 8, 10, and 11 under section 112, 1st paragraph, written description, all the claims stand or fall together.

## VIII. Argument

In the Final Rejection dated 03 June 2005, beginning at page 2, Claims 1, 3, 4, 7, 8, 10, and 11 were rejected under 35 U.S.C. § 112, 1st paragraph, as reciting subject matters that

allegedly fail to comply with the written description requirement. For at least the following reason, these rejections are in error and should be reversed.

*A. Legal Standard*

A claimed invention is unpatentable due to the lack of a written description if the specification fails to "clearly convey the information that an applicant has invented the subject matter which is claimed", *In re Barker* 559 F.2d 588, 592 (CCPA 1977), or if possession of what applicant claims as the invention is not put in the public domain. *See Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). To satisfy the written description requirement, possession must be shown; however possession alone does not cure the lack of a written description. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 1330 (Fed. Cir. 2002). For a claimed genus, the written description requirement may be satisfied through sufficient description of a representative number of species by disclosure of relevant identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of the above. See *Eli Lilly*, 119 F.3d at 1568. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. *See* M.P.E.P § 2163, II, A, 3, ii.

*B. The rejection of Claims 1, 3, 4, 7, 8, 10, and 11 under 35 U.S.C. § 112, 1st paragraph, written description, is in error*

Claims 1, 3, 4, 7, 8, 10, and 11 were rejected under section 112, 1st paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, were in possession of the claimed invention.

The claims of the present invention encompass a method for producing a heterologous protein comprising culturing a particular bacterium, a *Corynebacterium glutamicum* AJ12036

(FERM BP-734) bacterium, or mutant thereof, wherein said bacterium or mutant thereof have a genetic expression construct comprising a nucleic acid sequence encoding a signal peptide region from a coryneform bacterium which is downstream of a promoter sequence which functions in a coryneform bacterium, and a nucleic acid sequence encoding a heterologous protein which is downstream of said nucleic acid sequence encoding said signal peptide region, and recovering said heterologous protein, wherein said bacterium or mutant thereof is able to secrete the heterologous protein at least 2-fold higher than *Corynebacterium glutamicum* ATCC13869 having said genetic expression construct. Contrary to the explicit statement of the claim, however, the Office Action alleges on page 6 that "the claims as drafted encompass any mutant of the AJ12036 strain." Appellants respectfully disagree for the following reasons.

The claims encompass methods using the AJ12036 strain, and mutants thereof, wherein the bacterium (either the AJ12036 or mutants thereof) is able to secrete heterologous protein at least 2 fold higher than ATCC13869 which also contains the genetic construct. In other words and contrary to the assertion in the Office Action, not every mutant of strain AJ12036 is encompassed, but only those which retain the activity of being able to secrete heterologous proteins at the stated amount. The AJ12036 strain has this activity, and the claims encompass AJ12036-derived strains which have retained this activity, but otherwise might not be identical, *i.e.* mutants. The Office Action seems to imply that the person of skill in the art must be able to produce *de novo* mutants having the increased secretory production of proteins. However, since the mutant of the present invention is an AJ12036-derived mutant, *i.e.*, AJ12036 is the starting material or parent strain, one of skill in the art does not need to be able to generate ANY mutant which has the recited activity based upon the description in the specification, but merely must be able to recognize mutants derived from AJ12036, a very specific bacterium, which have retained that activity. Clearly, making such a determination is described in the specification and is within the skill of the ordinarily-skilled art worker.

It is well established that to adequately describe a claimed genus, a representative number of species encompassed by the genus must be implicitly or explicitly dislosed in the specification. To determine if a representative number of species is disclosed depends on

whether one of skill in the art would recognize that appellant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed. Appellants assert that they were in possession of the necessary common attributes or features of the elements possessed by the members of the genus, and that such possession is evident by appellants' specification. Specifically, since the "mutant thereof" must rely on the AJ12036 as a starting material, the genus is actually quite small, and it is clear that any "mutant thereof" must possess the common attribute of the activity of being able to secrete heterologous proteins at the stated amount. Determination of said activity at the stated amount is well described in the specification, and therefore, the mutants are clearly described.

The Final Rejection states that page 3, lines 14-17 of the specification discloses that mutants may include any strains obtained by mutagenesis and selection procedures for increased secretory properties. This seems to be referring to the last sentence of column [0026] in page 10; however, this section merely describes the generation of a mutant similar to AJ12036 from strains which do not have such a high secretion capacity, for example from the wild-type strain, that is, the *de novo* generation of a mutant having an increased capacity of secretory production of proteins at least 2-fold higher than the wild-type when the same genetic construct is introduced to them. Since the "mutant" referred to in Claim 1 is derived from an AJ12036 strain (the parent strain) which has the capacity of secreting proteins at least 2-fold higher than the wild-type, the "selection procedures" referred to by the Final Rejection will not be required to the extent that the Final Rejection asserts.

Again, the Appellant respectfully notes that recitation of "a mutant thereof" means a mutant which is obtained from AJ12036, using AJ12036 as the parent strain (a starting material). Namely, this recitation does not intend to encompass a mutant from a strain which does not have high secretion capacity, for example, from the wild-type strain. Although such mutants obtained from AJ12036 may be tested for the high capacity of secretory production, such a test will merely be a confirmation of the capacity to assure that high secretory production capacity of the parent strain (AJ12036) has not been lost.

The Final Rejection further alleges on page 4, lines 10-13 that "[w]hile the specification

provides broad guidance on methods of mutagenesis and selection which may be used to isolate mutant bacteria, there is no disclosure of the precise mutation of the AJ12036 coryneform bacteria useful for obtaining and/or maintaining the recited increased secretion properties." Since the mutant strains as claimed are limited to AJ12036 and a mutant thereof, which already has the desired activity, it is not necessary to specify mutations which will impart such activity to the AJ12036 mutants.

The Appellant believes that a mutant derived from AJ12036 will not lose the activity of being able to highly secrete heterologous proteins. Namely, a mutant which is derived from AJ12036 will also have the ability to secrete a heterologous protein at least 2-fold higher than the wild-type. This is because a random mutation would rarely introduce a mutation in the region responsible to this secretion capacity. For example, the mutation that caused the defect of producing a cell surface protein did not affect this high secretory production capacity, which is demonstrated in Example 9 in the specification.

For at least the foregoing reasons, Appellant respectfully submits that Claims 1, 3, 4, 7, 8, 10 and 11 fully comply with 35 U.S.C. § 112, first paragraph, and therefore respectfully requests withdrawal of the rejection thereof under 35 U.S.C. § 112.

*C. Claims 1, 3, 4, 7, 8, 10, and 11 are patentable and fully meet the written description requirement of 35 U.S.C. §112, 1st paragraph*

For at least the reasons presented herein, each of the subject matters of Claims 1, 3, 4, 7, 8, 10, and 11, taken as a whole, are patentable and meet the written description requirement of 35 U.S.C. §112, 1st paragraph. Accordingly, the rejection of each of Claims 1, 3, 4, 7, 8, 10, and 11 under section 112, 1st paragraph is reversible error.

## IX. Conclusion

For at least the foregoing reasons, Appellant respectfully submits that the subject matters of Claims 1, 3, 4, 7, 8, 10, and 11, each taken as a whole, are patentable. Accordingly, Appellant respectfully requests reversal of the rejections of Claims 1, 3, 4, 7, 8, 10, and 11 under section 112, 1st paragraph.

Respectfully submitted,

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Date: November 30, 2005

## APPENDIX A: CLAIMS ON APPEAL

1. A method for producing a heterologous protein comprising

A) culturing a *Corynebacterium glutamicum* AJ12036 (FERM BP-734) bacterium or mutant thereof having a genetic expression construct comprising a nucleic acid sequence encoding a signal peptide region from a coryneform bacterium which is downstream of a promoter sequence which functions in a coryneform bacterium, and a nucleic acid sequence encoding a heterologous protein which is downstream of said nucleic acid sequence encoding said signal peptide region, , and

B) recovering said heterologous protein,

wherein said bacterium or mutant thereof is able to secrete the heterologous protein at least 2-fold higher than *Corynebacterium glutamicum* ATCC13869 having said genetic expression construct.

3. The method of claim 1, wherein said mutant does not produce a cell surface protein .

4. The method of claim 1, wherein said signal peptide region comprises a signal peptide of a cell surface protein from a coryneform bacterium.

7. The method of claim 1, wherein said signal peptide region comprises a signal peptide of a cell surface protein from *Corynebacterium ammoniagenes*.

8. The method of claim 7, wherein said signal peptide comprises the amino acid sequence of SEQ ID NO: 3.

10. The method of claim 1, wherein said culturing of said bacterium or said mutant thereof is conducted in a medium containing at least 0.25 g/l (2.25mM) of calcium ion.

11. The method of claim 1, wherein said culturing of said bacterium or said mutant thereof is

conducted by controlling the dissolved oxygen concentration at 3% or less.

## APPENDIX B: EVIDENCE

None.

## APPENDIX C: RELATED PROCEEDINGS

None.